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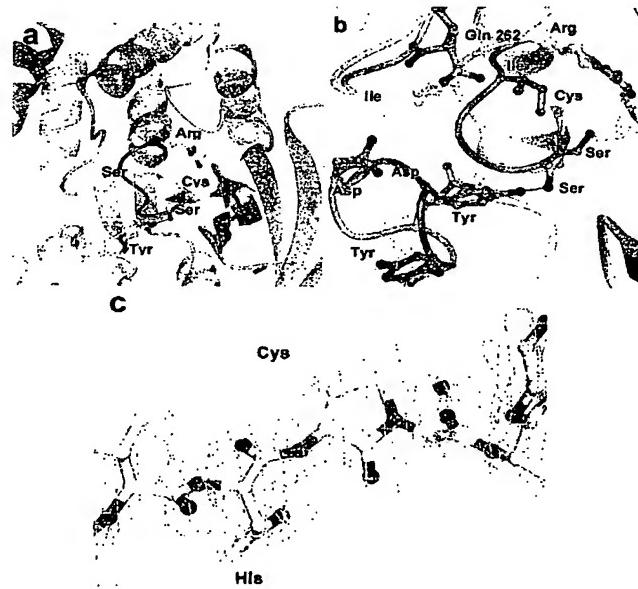
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- (81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

{Continued on next page}

(54) Title: PROTEIN TYROSINE PHOSPHATASE AND INHIBITORS THEREOF



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(57) Abstract: The invention provides novel inhibitors of protein tyrosine phosphatase sulfenyl amide and their use in medicine, for example in the treatment or prevention of disease states such as cancer, diabetes, rheumatoid arthritis and hypertension. Also provided are novel crystal structures and the use of the crystal structures and their X-ray coordinates in the development of new drugs.



(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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## INTERNATIONAL SEARCH REPORT

PCT/GB2004/001446

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C12N9/16 G06F17/50

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C12N G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DENU ET AL: "Specific and reversible inactivation of protein tyrosine phosphatases by hydrogen peroxide: Evidence for a sulfenic acid intermediate and implications for redox regulation"  <b>BIOCHEMISTRY</b>,    vol. 37, 1998, pages 5633-5642,    XP002247280    * See pages 5633-34 (Introduction / Cys-SOH intermediate) *</p> <p style="text-align: center;">-/-</p>	1-8, 11, 13-46, 84-94

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## ° Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the international search report
29 September 2004	11/10/2004
Name and mailing address of the ISA European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax. (+31-70) 340-3016	Authorized officer  Korsner, S-E

## INTERNATIONAL SEARCH REPORT

PCT/GB2004/001446

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SALMEEN ET AL: "Redox regulation of protein tyrosine phosphatase 1B involves a sulphenyl-amide intermediate" NATURE, vol. 423, 12 June 2003 (2003-06-12), pages 769-773, XP002298318 * See the whole document (the same Cys-215 modification); note the PDB references 1OEM and 1OE0 (release date = 12.06.03) on page 773 *	1-8,11, 13-46, 84-94
P,X	VAN MONTFORT ET AL: "Oxidation state of the active-site cysteine in protein tyrosine phosphatase 1B" NATURE, vol. 423, 12 June 2003 (2003-06-12), pages 773-777, XP002298319 * A disclosure by the inventors; note the PDB references 1OES, 1OET, 1OEU and 1OEV (release date = 12.06.03) on page 777) *	1-8,11, 13-46, 84-94
L	TAYLOR ET AL: "Potent non-peptidyl inhibitors of protein tyrosine phosphatase 1B" BIOORGANIC ET MEDICINAL CHEMISTRY, vol. 6, 1998, pages 1457-1468, XP000990565 * See the different types of inhibitors *	1-8,11, 13-46, 84-94
L	TAYLOR: "Inhibitors of protein tyrosine phosphatase 1B (PTP1B)" CURRENT TOPICS IN MEDICINAL CHEMISTRY, vol. 3, 2003, pages 759-782, XP009013861 * Late-published review but most references are prior art -> see the different types of inhibitors *	1-8,11, 13-46, 84-94

**INTERNATIONAL SEARCH REPORT**

PCT/GB2004/001446

**Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of Item 1.b of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the International application and necessary to the claimed invention, the International search was carried out on the basis of:
  - a. type of material
    - a sequence listing
    - table(s) related to the sequence listing
  - b. format of material
    - in written format
    - in computer readable form
  - c. time of filing/furnishing
    - contained in the International application as filed
    - filed together with the International application in computer readable form
    - furnished subsequently to this Authority for the purpose of search
2.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

## **INTERNATIONAL SEARCH REPORT**

PCT/GB2004/001446

**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
  2.  Claims Nos.: **9-10, 12, 47-83**  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.: \_\_\_\_\_
  4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: It is covered by claims Nos.: \_\_\_\_\_

## **Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although Claims 13-22, 44-46, 82-83 are (at least implicitly) directed to a method of treatment, the search has been carried out and based on the alleged effects of the compounds.

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Continuation of Box II.2

Claims Nos.: 9-10,12,47-83

Claims 9-10,12,47-83 relate to compounds defined by reference to a desirable property.

The Application does not provide technical support for a single inhibitor - but only lists a large number of possible structures.

The statement in Claim 47 ("A novel compound per se...") is irrelevant and also disregards the fact that any compounds must be inventive too. Similarly, the reference to a certain structure (3D) is by no means a sufficient disclosure of useful compounds.

These claims are therefore considered as desiderata and no search has been made. Nonetheless, two L-documents have been included for information.

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The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.